Cambridge City Publishers

Case Reports in Clinical Cardiology Journal

Case Report | Vol 4 Iss 1

Successful R0 Resection of Right Atrial Metastasis in a Patient with Cervical CUP Syndrome

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Received: January 03, 2024; **Accepted:** January 28, 2024; **Published:** February 05, 2024

Abstract

Background: Carcinoma of Unknown Primary (CUP) syndrome is a rare and complex oncological challenge characterized by an unidentified primary site, accounting for 1-2% of invasive cancers. Secondary cardiac involvement in cancer is more common, often driven by metastasis, and is associated with various malignancies.

Case Presentation: A 64-year-old male with CUP syndrome initially presented with right cervical tumor. Histological examination revealed a poorly differentiated squamous cell carcinoma with high PD-L1 expression. The subsequent PET-CT showed a malignancy-suspect lesion in the free right atrial wall. According to the tumor board decision, the tumor was completely resected and the right atrial wall and the superior vena cava were reconstructed using bovine pericardium. The post-operative course was uneventful and the patient was discharged on postoperative day 9. The final diagnosis was a poorly differentiated squamous cell carcinoma in the right atrium.

Conclusion: This case emphasizes the importance of a multidisciplinary approach, combining clinical evaluation and advanced imaging, in managing complex scenarios of CUP with secondary cardiac malignancies. Ongoing research and standardized diagnostic and treatment approaches are needed for these rare and intricate clinical presentations. Accumulating more cases and data is essential to improve the understanding and management of such complex conditions, potentially including emerging therapies like immune checkpoint inhibitors.

Keywords: Carcinoma of unknown primary; CUP syndrome; Secondary cardiac involvement; Right atrial metastasis; Multidisciplinary approach; Immune checkpoint inhibitors

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Introduction

The heterogeneity of CUP syndrome makes diagnosis challenging. CUP occurs in 2-4% of all invasive cancers [1,2]. In many cases, the primary site remains unidentified, even after extensive clinical and pathological assessments. In this constellation, CUP is diagnosed through the biopsy of metastatic lesions, only after specific diagnostic tests fail to identify the primary site. When an anatomic primary site is found in a patient with CUP, they are no longer classified as having CUP, and treatment is tailored to the identified tumor type, adhering to established guidelines [1-3].

Primary cardiac tumors are exceedingly rare, with an incidence of approximately 0.02%. In contrast, secondary cardiac involvement, often driven by metastatic spread, occurs more frequently [4]. This can essentially be attributed to various factors, including the continuous motion of the myocardium, the unique metabolic characteristics of striated cardiac muscle, the rapid circulation of blood within the heart, and the lymphatic flow moving away from the heart [5].

The clinical expression of cardiac tumors is affected by their location within the heart, rather than their histopathological characteristics [6]. Notably, tumors originating in the right atrium can obstruct blood flow, leading to hemodynamic changes similar to tricuspid stenosis. Clinical manifestations predominantly resemble right heart failure. Furthermore, tumor fragments released in the pulmonary circulation can cause pulmonary artery embolism [7]. Right atrial hypertension may result in venous blood shunting into the systemic circulation, causing hypoxemia or systemic emboli when a patent foramen ovale or atrial septal defect is present [8,9].

Cardiac metastases occur relatively frequently, with malignancies such as malignant melanoma, lung cancer, breast cancer, soft tissue sarcomas, renal carcinoma, esophageal cancer, hepatocellular carcinoma, thyroid cancer, leukemia, and lymphoma being associated with secondary cardiac involvement [10-12].

The present case serves as a bridge between the enigmatic realm of CUP syndrome and the unique manifestation of secondary cardiac involvement, particularly within the right atrium. It highlights the diagnostic challenges, management strategies, and the prospects for tailored therapy in the context of CUP with right atrial metastasis.

Case Presentation

A 64-year-old male patient presented with a medical history notable for a diagnosis of Carcinoma of Unknown Primary (CUP) syndrome, initially identified in January 2021. The primary manifestation of this syndrome included right-sided cervical metastasis. In February 2021, the patient underwent a comprehensive evaluation, which included panendoscopy and modified radical neck dissection involving levels II/III on the right side. During this procedure, four lymph nodes were excised, with the largest measuring up to 48 mm. The initial staging was described as cT0, pN3b (4/7, ece+), cM0, and Grade 3. Following surgery, the patient underwent a course of radiochemotherapy comprising 29 cycles of cisplatin between March and April 2021.

Histopathological analysis of the excised lymph nodes revealed strong expression of cytokeratin 8/18, 5/14, and p63, while markers such as cytokeratin 7, p53, p16, androgen receptor, smooth muscle actin, MYB, and Her2/neu were all negative. The proliferation rate, assessed using Ki-67, was found to be 80%. Immunohistochemistry for PD-L1 (Ventana SP 263) revealed a tumor Proportion Score (TPS) of 95, Combined Positive Score (CPS) of 100, and an Immune Cell (IC) score of 3. The

histopathological report confirmed the presence of lymph node metastasis involving low-differentiated squamous epithelial carcinoma, with evidence of tumor growth penetrating the lymph node capsule. Importantly, no involvement of salivary glands was noted.

In August 2022, a follow-up Positron Emission Tomography-Computed Tomography (PET-CT) scan showed no evidence of recurrence in the neck region. However, an indeterminate lesion in the vicinity of the right atrium was observed, characterized by partial contrast medium recess in the right atrial appendage with increased metabolic activity (SUVmax 10.1, VU 4.8). A differential diagnosis of a thrombogenic process was considered, and echocardiography was recommended.

Subsequent evaluations in September 2022, including transthoracic echocardiography, yielded normal results. However, in October 2022, a computed tomography of the thorax revealed again this tumor in the same location, with dimensions consistent with those observed on PET-CT.

In November 2022, cardiac magnetic resonance imaging (CMR) indicated the presence of a soft tissue space-occupying lesion within the right atrium. This lesion measured 2.5 cm ventrodorsally, 2.2 cm laterolaterally, and 2.1 cm craniocaudally. The lesion displayed intermediate T2 signal intensity, hyperintensity on T2 fat saturation images, and myocardial isodensity on T1-weighted imaging. No infiltration into neighboring fatty tissue or the pericardium was evident, and no pericardial effusion was observed. While intracardiac metastasis was highly probable, the diagnosis of angiosarcoma was considered unlikely. Preoperative coronary angiography conducted in December 2022 revealed mild coronary artery disease (CAD) involving a 60% stenosis in the right coronary artery (RCA).

In December 2022, the patient underwent cardiac surgery to resect the tumor. Intraoperatively, the entire right atrium was found to be filled with a solid tumor characterized by relatively smooth borders. The tumor had infiltrated the wall of the right atrial appendage, as well as the medial and lateral walls of the adjacent atrium and the roof of the superior vena cava. The tumor was excised, preserving a safety margin of 1-1.5 cm from the infiltrated structures. The resected specimen was subjected to frozen section diagnosis, which confirmed the presence of a malignant tumor, most likely being a sarcoma. Importantly, the resection margins were free of tumor (R0 resection). The cardiac defect was closed using a bovine pericardial patch and 4.0 prolene running suture. Following surgery, the patient was transferred to the intensive care unit for one day and after unremarkable post-operative course, was discharged on post-operative day 9 without evidence of disease. Subsequent recommendations included regular PET/CT surveillance every three months to monitor disease progression and evaluate the potential for immune checkpoint therapy based on PD-L1 status. 11 months after discharge, contact with the patient revealed that he is currently symptom free, has no signs of recurrence, and subsequently in no need for further therapy.

The preliminary pathology report described the tumor as a pleomorphic, mitotically active, necrotizing malignancy accompanied by a chronic lymphoplasmacytic inflammatory cell infiltrate. The minimum distance from the tumor to the resection area through the myocardium was 0.4 cm, and the pericardium displayed reactive pleurisy with mesothelial hyperplasia. Pre-aortic lymph nodes were structurally unremarkable and free of tumor involvement, with minimal anthracosis noted.

The final immunohistological profile of the tumor demonstrated positivity for CK AE 1/3, CK 5/6, P40, and a subset of cells positive for Vimentin. The proliferation rate, as measured by Ki-67, was approximately 60%. Weak expression of P53 was observed in individual tumor cells, making it challenging to ascertain a mutation-specific expression profile. Tumor cells were negative for CD31, ERG, CD34, S100, P16, CK 7, CK 20, Caldesmon, SMA, TLE1, and MDM2. Additionally, in CD20 immunohistochemistry, a reactive follicle-forming inflammatory B-cell infiltrate was noted, along with intercepted T cells in CD3 immunohistochemistry. In Situ Hybridization for EBER-CISH revealed occasional positive signals, but the tumor was predominantly negative. Taken together, the immunohistochemical profile supported the diagnosis of a poorly differentiated, p16-negative squamous cell carcinoma within the right atrium.

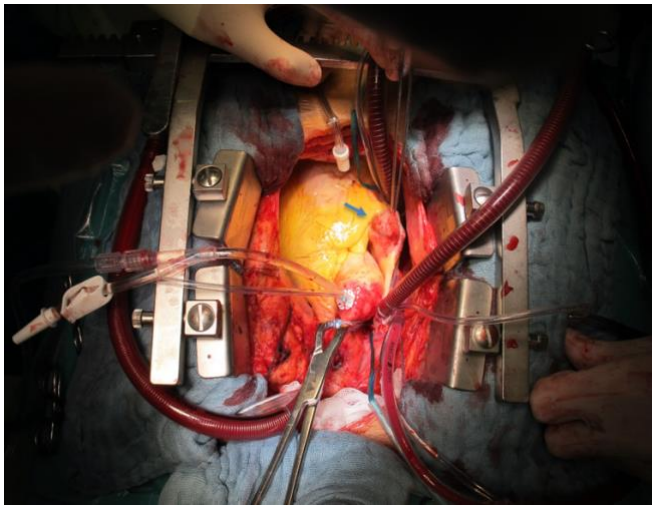

Figure 1: Tumor before resection (arrow).

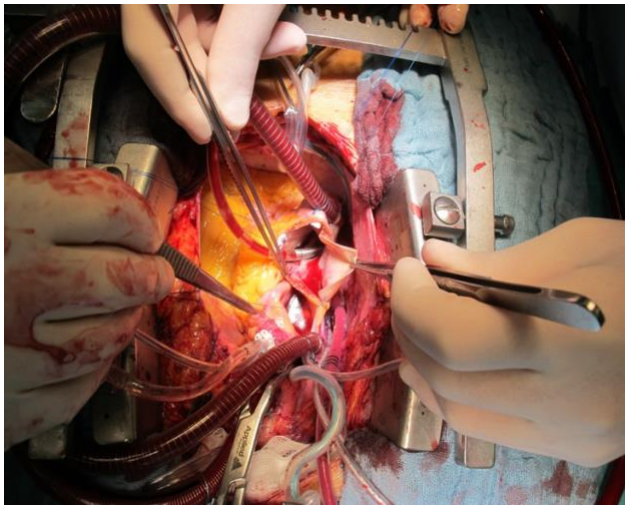

Figure 2: Tumor resected with begin of patch closure.

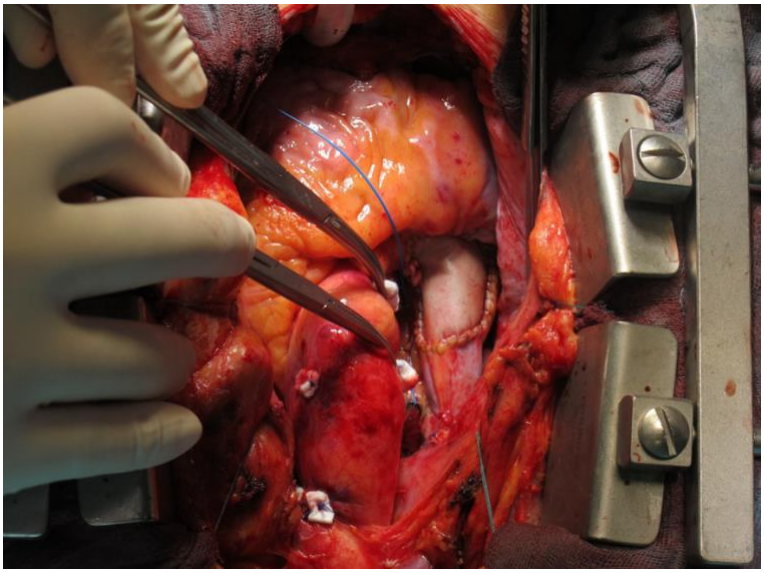

Figure 3: Result after completed Patch reconstruction of right atrium and adjacent SVC.

Discussion

The present case report illustrates the complex diagnostic journey of a 64-year-old male patient initially diagnosed with CUP syndrome, primarily characterized by right-sided cervical metastasis. Despite an extensive evaluation, the anatomic primary site remained unknown, underscoring the enigmatic nature of CUP. Histopathological analysis of excised lymph nodes revealed a unique immunohistochemical profile, including strong expression of cytokeratin markers, p63, and a high proliferation rate (Ki-67 80%). The exceptional expression of PD-L1 with a TPS of 95 and CPS of 100 posed intriguing prospects for future immune checkpoint therapy. The patient's course took an unexpected turn when a nonspecific lesion within the right atrium was detected requiring extensive diagnostics and evaluation.

In the clinical assessment of patients with suspected cardiac involvement, the primary objectives of the initial diagnostic evaluation are to determine the presence of a cardiac tumor, precisely locate the lesion within the heart, and, to the best extent possible, distinguish between benign and malignant tumors. Cardiac imaging modalities, such as echocardiography, CMR, cardiac computed tomography, and PET, are essential in providing comprehensive insights to address these important questions, and they are employed selectively based on the patient's clinical presentation [13-16]. Notably, PET has proven to be a valuable tool in the identification of cardiac involvement in patients with metastatic tumors [17,18]. However, the competent interpretation of PET findings is indispensable to effectively differentiate between malignant and benign causes of focal uptake within the heart [19].

The prudent use of these imaging techniques provides the precise characterization of cardiac tumors, which, as seen in the present case, can be diverse in their histopathological features and clinical implications. Moreover, the technological progress in diagnostic imaging modalities provides a more refined understanding of the tissue characteristics, aiding in the differentiation between primary and secondary cardiac tumors and assisting in the formulation of tailored treatment strategies. Metastatic involvement of the heart or pericardium should be considered when a patient with a known malignancy shows symptoms such as pericardial effusion, cardiovascular symptoms, or the presence of new or changing heart murmurs, electrocardiographic conduction delays, or arrhythmias [20]. Also, cardioembolic events may indicate a cardiac tumor, even if rare. In some rare instances, cardiac metastases may manifest as the initial sign of malignancy [20].

In December 2022, the patient underwent cardiac surgery, revealing a solid tumor infiltrating the right atrial appendage and adjacent atrial walls, which was subsequently identified as a pleomorphic, mitotically active, necrotizing malignancy. The further diagnostic path was complicated by challenges in discerning the tumor's exact histopathology due to weak expression of P53 and the absence of specific markers like CD31, ERG, CD34, and S100. The final diagnosis suggested a poorly differentiated, p16-negative squamous cell carcinoma within the right atrium.

Limitations

While this case provides valuable insights into the diagnosis and management of CUP with secondary right atrial metastasis, certain limitations should be acknowledged. These limitations include the rarity of both CUP and secondary cardiac tumors, the heterogeneity of CUP, the complexity of diagnosis, the interpretative challenges of imaging techniques, and the lack of specific treatment guidelines. This underscores the need for more comprehensive studies, standardized diagnostic and treatment

approaches, and further exploration of emerging therapies to address these intricate clinical scenarios. Ongoing research is crucial to enhance our understanding and improve the management of these complex medical conditions.

Conclusion

The multidisciplinary approach to diagnosis, clinical evaluation and advanced imaging techniques are essential for resolving complex scenarios where CUP syndrome coincides with the development of secondary cardiac malignancies. Surgery plays an important role in the treatment plan either for histological analysis, for tumor debulking or as in this case, complete tumor resection with curative approach. Furthermore, considering the rarity of both CUP and secondary cardiac tumors, the accumulation of more cases and data is vital to achieve a better understanding of these complex conditions. This understanding is crucial for the refinement of treatment approaches and the potential integration of emerging therapies, such as immune checkpoint inhibitors, in the management of such challenging cases.

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